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INCORPORATION OF SIMETHICONE INTO SYRUPY OR CLEAR BASE LIQUID ORALS

By

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ABSTRACT

The objective of this project was to incorporate simethicone in a syrupy or clear base liquid oral.

Best results were obtained when a commercially available emulsion concentrate was stabilized with Carbopol® resins. The use of 0.2% neutralized Carbopol® resin in combination with glycerin and propylene glycol produced a very stable formulation which did not show any separation or creaming for the duration of the studies.

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INTRODUCTION

Simethicone, an antiflatulant, is a viscous, translucent, odorless and tasteless fluid which is insoluble in water, alcohol and other solvents commonly used in liquid orals[1,2]. The formulation of simethicone into an aesthetically elegant clear base, however, is extremely difficult in view of the physicochemical characteristics of simethicone.

Reports in the literature address the incorporation of simethicone in ointments, dermatological preparations[3], tablets[4,5], suspensions[4], and cosmetic formulations[4,6], but no comparable reports on its incorporation into syrup or clear liquid vehicles. We studied three different approaches to prepare clear base liquid preparations of simethicone: a solution using a cosolvent system; an emulsion with internal and external phases with similar indices of refraction so that the product appears clear; and a gel stabilizer possessing similar indices of refraction.

MATERIALS AND METHODS

This study consisted of two parts: 1) preparation of different formulations; and 2) evaluation of their stability.

Formulation Evaluation:

Criteria 1: When freshly prepared, the product should be uniform to the naked eye.

Criteria 2: If Criteria 1 was satisfied, the product should remain physically stable at room temperature for 15 days.

Criteria 3: If Criteria 1 was satisfied, then the product should remain physically stable at 45°C for 5 days. This study was done in closed 100 ml graduated cylinders. Microscopic examination was repeated at the end of the room temperature study if Criteria 2 was satisfied and at the end of the 45°C study if Criteria 3 was satisfied. Also, if Criteria 1, 2 and 3 was

satisfied, then centrifugation was used as a means to compare different formulations.

Studies for Criteria 2 and 3: The formulation was evaluated for breaking and creaming. In order to minimize subjectivity of observations, breaking and creaming was quantified on a scale from 1 to 5 as follows : 1 = satisfactory condition; 2 = slight inhomogeneity; 3 = beginning of creaming; 4 = noticeable creaming; and 5 = separated/creamed product.

Criteria 2 and 3 were satisfied if there was no breaking, and any creaming could be redispersed on shaking. Redispersion was to be done only at the end of the study, i.e., at the end of 15 days at room temperature (25°C) and at the end of 5 days at 45°C.

Preparation of Formulations: Simethicone, as well as commercially available concentrated (30%) emulsions, were used in the study[7-10]. All formulations were to exhibit the following common features, unless otherwise indicated: (1) All formulations were done in duplicate; (2) Simethicone was used in a concentration of 40 mg per 5 ml.; (3) Amaranth was used as a coloring agent in a concentration of 0.001% to aid in the visual examination of any physical instability or separation; (4) A hand-mixer[11] was used for initial mixing followed by homogenization using an Erweka[12] homogenizer for a period of 3 minutes.

The various approaches used have been classified under subheadings. These experiments have been summarized in Table I.

Use of Tweens and Spans: The first attempt involved the use of Tween to study whether or not Tween 80[13] would cause emulsification of simethicone at higher concentrations (Formulations 1 and 2). In Formulation No. 3, a combination of Tween 80 and Span 80[14] was used. The liquid vehicle was modified to include 20% glycerin[15] to increase viscosity for better stability.

TABLE 1

Formulations Using Tween 80 and Span 80

Batch Size: 300 ml

Formula:

Simethicone	2.4 g
Amaranth	3.0 mg
Emulsifying Agent	As per Table
Liquid Vehicle, qs	300 ml

Formula Number	Emulsifying Agent/Conc.	Liquid Vechicle	Remarks	Passed Criteria 1-3	Failed in Criteria	Centrifuge Test
1	Tween 80 0.4%	Water	-	No	1	No
2	Tween 80 0.8%	Water	-	No	1	No
3	Tween 80 0.4% Span 80 0.4%	Glycerin 20% in water	Combination reported effective	No	1	No
4	Tween 80 0.4% Span 80 0.4%	Glycerin 20% in water	Primary emulsion formed first	No	1	No
5	Tween 80 0.4% Span 80 0.4%	Glycerin 20% in water	Primary emuls. using Dow Corning Fluid 200	Yes		Yes
6	Tween 80 0.4% Span 80 0.4% Glyceryl monost. 1.0% Sod. lauryl sulfate 0.1%	Glycerin 20% in water	Emulsion stabilizer included	No	1	No

Another modification involved a change in the technique of emulsification. Thus, in Formulation No. 4 and 5, a primary emulsion was formed first. The above Formulation No. 5 used Dow Corning Fluid 200. This fluid is much less viscous (500 cps at 25°C) than the simethicone so we could study the effect of viscosity on formulation.

Another formulation (No. 6) involved the incorporation of glyceryl monostearate[16] and sodium lauryl sulfate (SLS)[17] as emulsion stabilizers. Glyceryl monostearate was melted and mixed with SLS, Tween 80, Span 80, and simethicone and this mixture added to the aqueous phase as in Formulation No. 3.

Use of Silica as an Adsorbent: Another method was to incorporate simethicone in a 40% solution of glycerin in water by first adsorbing it on SYLOID® 244 FP[18] (Formulation No. 7).

Use of G-Emulsifiers: G-Emulsifiers[19], polyoxyethylene lanolin derivatives, are commercially available and have been reported as good emulsifiers [3]. Simethicone 0.8% (2.4 g) in a 300 ml batch size was used and the following two blends of emulsifying agents tried: Formulation No. 8 was G-1471, 0.25%, G-1790 0.25%, and G-2162 0.25%. Formulation No. 9 was G-2162 0.40% and G-1441 0.40%.

Use of Nonaqueous Parenteral Solvents: Spiegel and Noseworthy[20], in their review of nonaqueous solvents used in parenteral products, cited a number of solvents that might be useful in oral liquids. Some water soluble solvents selected from this review were used (Table 2).

Use of Brij® Emulsifiers: Experiments were done to emulsify simethicone using Brij® surfactants listed in Table 3. Equal parts of Brij® 30 (HLB 9.5)[21] and Brij® 35 (HLB 16.9)[22] were used as the emulsifying agents in Formulations 17 and 18. In Formulation No. 19, a primary emulsion of simethicone was made first. Formulation No. 20 used Dow Corning Fluid 200.

Use of Different Liquid Vehicles: Another series of experiments involved evaluating the stability of

TABLE 2

Formulations Using Nonaqueous Solvents

Formula:	Simethicone	2.4 g
	Amaranth	3.0 mg
	Emulsifying Agent	None
	Liquid Vehicle, qs	300 ml

Formula Number	Liquid Vehicle	Criteria 1-3	Failed in Criteria	Centrifuge Test
10	Glycerol formal 50% in water	No	1	No
11	Butanediol 50% in water	No	1	No
12	Dioxolane 50% in water (Isopropylidene glycerol)	No	1	No
13	Hydroxyethyl lactamide 50% water	No	1	No
14	Ethyl lactate 50% in water	No	1	No
15	Dimethylacetamide 50% in water	No	1	No
16	10% each of #10 to #15 and 40% water	No	1	No

TABLE 3

Formulations Using Brij Surfactants

Formula: Simethicone 2.4 g
Amaranth 3.0 mg
Emulsifying Agent As per Table
Liquid Vehicle, qs 300 ml

Formula Number	Emulsifying Agent/Conc.	Liquid Vehicle	Remarks	Passed Criteria 1-3	Failed in Criteria	Centrifuge Test
17	Brij 30 0.2% Brij 35 0.2%	Glycerin 40% in water	-	No	1	No
18	Brij 30 0.4% Brij 35 0.4%	Glycerin 40% in water	Increased concentration	No	1	No
19	Brij 30 0.4% Brij 35 0.4%	Glycerin 40% in water	Primary emulsion formed first	Yes		Yes
20	Brij 30 0.4% Brij 35 0.4%	Glycerin 40% in water	Primary emulsion using Dow Corning Fluid 200	Yes		Yes

simethicone emulsions formed using Brij surfactants in different liquid vehicles are listed in Table 4.

Use of Dow Corning Medical Antifoam AF Emulsion: Dow Corning Medical Antifoam AF emulsion is a viscous creamy 30% simethicone emulsion which was used with the different liquid vehicles used earlier for the Brij emulsion (Table 4). Table 5 contains a list of the formulations made in this manner.[23]

Use of Union Carbide SENTRY® Emulsion: Union Carbides' SENTRY® emulsion is a white 30% simethicone emulsion which was used in a similar manner as listed in Table 6.

Centrifugation Studies: Formulations which satisfied Criteria 1, 2 and 3 were subjected to centrifugation in screw-capped glass tubes at 3000 rpm for 20 minutes using a Beckman Model TJ-6 centrifuge[24] ("g" value 1530).

RESULTS

Tweens and Spans are conventionally used as emulsifying agents both singularly and in combination. A combination of both has been reported to cause self-emulsification of oils[25]. Also, since the technique of emulsification is as important as the emulsifying agent itself, the preparation technique was also modified while keeping the formula the same. It was observed that making a primary emulsion first helped improve formulation stability and a low viscosity simethicone could be more easily dispersed. As a result, only Formulation No. 5, passed Criteria 1.

SYLOID micron-sized silicas have been reported to adsorb internally up to three times their own weight of many liquids by virtue of their large surface area. They are odorless, tasteless, finely-divided, amorphous powders with a refractive index (1.46) similar to many liquids such as glycerin and sorbitol, which makes them invisible in these liquids. Formulation No. 7 passed Criteria 1 and microscopic observation showed a diffuse structure rather than any discrete dispersed simethicone droplets, indicating that simethicone was adsorbed onto

TABLE 4

Incorporation of Brij Primary Emulsion in Different Liquid Vehicles

Simethicone primary emulsion made as per Formulation No. 19 was diluted to 30% strength and incorporated in different liquid vehicles.

Formula:

Brij Simethicone emulsion 30% equivalent to Simethicone 0.8%	8.0 g
Amaranth	3.0 mg
Liquid Vehicle as per Table, qs	300 ml

Formula Number	Liquid Vehicle		Remarks	Passed Criteria 1-3	Failed in Criteria	Centrifuge Test
21	Syrup NF		-	No	2 & 3	No
22	Glycerin 50% in water		-	No	2 & 3	No
23	Glycerin	20%	The combination may have some cosolvency or solubilization effect	No	2 & 3	No
	Propylene Glycol	10%				
	Syrup NF	15%				
	PEG 400	10%				
	Ethanol	5%				
	Water	40%				
24	Carbopol 934	0.1%	Sodium hydroxide neutralization	Yes		Yes
25	Carbopol 934	0.2%	As above	Yes		Yes
26	Carbopol 934	0.2%	As above	Yes		Yes
	Glycerin	20.0%				
	Propylene Glycol	20.0%				
	Walter	60.0%				
27	As above		Triethanolamine neutralization	Yes		Yes
28	As above		No neutralization	Yes		Yes

TABLE 5

Incorporation of Commercial Dow Corning Medical Antifoam AF Emulsion in Different Liquid Vehicles

Formula:

Dow Corning Medical Antifoam AF Emulsion equivalent to Simethicone 0.8%	8.0 g
Amaranth	3.0 mg
Liquid Vehicle as per Table, qs	300 ml

Formula Number	Liquid Vehicle		Remarks	Passed Criteria 1-3	Failed in Criteria	Centrifuge Test
29	Syrup NF		-	No	3	No
30	Glycerin 50% in water		-	Yes		Yes
31	Glycerin	20%	The combination may have some cosolvency or solubilization effect.	Yes		Yes
	Propylene Glycol	10%				
	Syrup NF	15%				
	PEG 400	10%				
	Ethanol	5%				
	Water	40%				
32	Carbopol 934	0.1%	Sodium hydroxide neutralization	Yes		Yes
33	Carbopol 934	0.2%	As above	Yes		Yes
34	Carbopol 934	0.2%	As above	Yes		Yes
	Glycerin	20.0%				
	Propylene Glycol	20.0%				
	Water	60.0%				
35	As above		Triethanolamine neutralization	Yes		Yes
36	As above		No neutralization	Yes		Yes

TABLE 6

Incorporation of Commercial Union Carbide SENTRY Emulsion in Different Liquid Vehicles

Formula: Union Carbide SENTRY Emulsion 30% equivalent to Simethicone 0.8% — 8.0 g
Amaranth — 3.0 mg
Liquid Vehicle as per Table, qs — 300 ml

Formula Number	Liquid Vehicle		Remarks	Passed Criteria 1-3	Failed in Criteria	Centrifuge Test
37	Syrup NF		-	No	3	No
38	Glycerin 50% in water		-	Yes		Yes
39	Glycerin	20%	The combination may have some cosolvency or solubilization effect	Yes		Yes
	Propylene Glycol	10%				
	Syrup NF	15%				
	PEG 400	10%				
	Ethanol	5%				
	Water	40%				
40	Carbopol 934	0.1%	Sodium hydroxide neutralization	Yes		Yes
41	Carbopol 934	0.2%	As above	Yes		Yes
42	Carbopol 934	0.2%	As above	Yes		Yes
	Glycerin	20.0%				
	Propylene Glycol	20.0%				
	Water	60.0%				
43	As above		Triethanolamine neutralization	Yes		Yes
44	As above		No neutralization	Yes		Yes

micron-sized silica particles. On continued observation the formulation showed creaming that was easily redispersed. The physical stability presented an unusual feature in the sense that the dispersed colloid split up into two parts - one rising to the top and the other settling to the bottom with clear liquid in between.

Formulations 8 through 18 failed to meet Criteria 1 and were not further evaluated.

Brij surfactants are a series of emulsifying agents reported to be effective in the emulsification of silicone oils in dermatological vehicles. Successful formulations could be made (19 and 20) if a primary emulsion was formed first. Formulations made using Dow Corning Fluid 200 exhibited very good physical stability.

Simethicone primary emulsions made using Brij surfactants were then evaluated for physical stability in different liquid vehicles. All formulations (21-28) were stable at the time of preparation since a preformed primary emulsion was used. However, behavior during the 25°C (RT) and 45°C study depended on the nature of the liquid vehicle.

Formulations 21 through 23, using syrup or 50% glycerin showed physical instability. Addition of other solvents such as propylene glycol, PEG 400, etc., to glycerin (Formulation No. 23) did not improve stability.

The remaining formulations used preformed liquid phases and, as such, satisfied Criteria 1 and were further evaluated.

Carbopol® resins are excellent emulsion stabilizers and maintain their viscosity at temperatures approaching 60°C, effectively keeping dispersed phase droplets immobilized and maintaining emulsion integrity. Excellent results were obtained by using 0.2% Carbopol® resin in conjunction with glycerin and propylene glycol (Formulation No. 26). This formulation did not require redispersion at the end of the study as no separation

was observed. In other Carbopol® formulations, some creaming was observed, but it was easily redispersed.

Effect of Centrifugation: Centrifugation of formulation formulations resulted in the creaming and/or coalescence of the low volume dispersed phase (simethicone) which separated out as a thin whitish layer on top. All separated in the manner described except for Formulations No. 30, 34, 35, 41, 42 and 43, which were made by stabilizing commercial simethicone emulsion with Carbopol® resin.

Microscopic Studies: Little variation was observed in the particle size at the end of the 25°C (RT) and 45°C study periods.

CONCLUSIONS

Different formulations and techniques were used to prepare a clear liquid product of simethicone. Of these, Syrup NF, exhibited the greatest physical stability problem as the product could not be redispersed after the study period. Excellent results were obtained using 0.2% Carbopol® in combination with glycerin and propylene glycol and formulations similar to this should be further studied.

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